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1,3-Dipolar cycloadditions of fluorinated nitrones with thioketones

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ABSTRACT

Fluorinated nitrones derived from fluoral and difluoroacetaldehyde react with thioketones via [3+2] cycloaddition yielding 1,4,2-oxathiazolidines in a regioselective manner. Unexpectedly, cycloaliphatic thioketones react faster than aromatic thioketones. Due to the presence of a fluorinated alkyl group, the cycloadducts display a remarkable stability and do not decompose at room temperature in the crystalline form nor in solution.

1. Introduction

A general and widely applied method for the preparation of five-membered heterocycles is the 1,3-dipolar cycloaddition [1]. Among the N-containing 1,3-dipoles, nitrones form an important class, and they are well known to undergo reactions with diverse dipolarophiles such as activated and non-activated C=C and C≡C bonds [2]. According to Sustmann's classification of 1,3-dipoles, nitrones belong to the so-called type II, i.e., the concerted cycloaddition step occurs via $LUMO_{Dipole}$ –$HOMO_{Dipolarphile}$ as well as via $HOMO_{Dipole}$ –$LUMO_{Dipolarophile}$ interactions [3].

In the last two decades, thioketones have attracted attention as extremely reactive dipolarophiles, and based on a reactivity scale towards 1,3-dipoles such as nitrones, diazoalkanes and thiocarbonyl ylides, they were named as 'superdipolarophiles' [4].

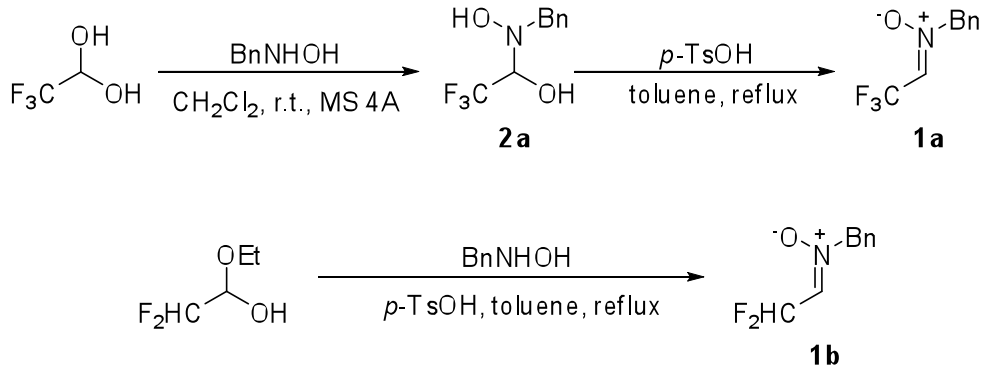
Fluorinated nitrones are a lesser-known group of nitrones. From the point of view of potential applications for the synthesis of fluorinated heterocycles, nitrones of type **1,** derived from fluorinated acetaldehydes, are of special interest. However, reports on their preparation and reactivity are scarce. The first syntheses of *N*-phenyl- and *N*-(tert-butyl)nitrones of type **1** were performed by treatment of the corresponding nitroso compound with 2,2,2-trifluorodiazoethane [5]. Practically useful protocols are based on the reactions of fluoral hydrate or fluoral hemiacetals with *N*-alkyl hydroxylamines [6]. The latter method corresponds to the general approach to nitrones.

An extended study on the 1,3-dipolar cycloadditions of the *N*-methyl-substituted nitrone of type **1**, derived from fluoral, was carried out using alkynes and alkenes as dipolarophiles [6a,b]. It is worth mentioning that, typically for 1,3-dipoles of type II, this nitrone reacted with both electron-deficient and non-activated alkynes and alkenes yielding 3-trifluoromethyl isoxazole derivatives. To the best of our knowledge, there are no reports of 1,3-dipolar reactions of nitrones, derived from fluorinated acetaldehydes, with hetero-dipolarophiles.

In a recent paper, we described a new application of fluoral carbohydrazones for the synthesis of diverse five-membered heterocycles via addition/cyclization procedures [7]. Due to our ongoing interest in the exploration of thioketones for the synthesis of *S*-containing heterocycles [4d,8], we decided to apply them for 1,3-dipolar cycloadditions with fluorinated nitrones.

2. Results and discussion

The fluorinated nitrones **1a** and **1b** used in the present study were prepared by reacting the corresponding aldehyde hydrate (in the case of **1a**) or ethylhemiacetal (for **1b**) with *N*-benzyl hydroxylamine, followed by dehydration of the initially formed aminals [6]. In the case of **1a**, a significant enhancement of the yield was achieved via the two-step procedure. The first step was carried out in dichloromethane at room temperature to give the nitrone hydrate **2a**. The subsequent dehydration was performed in boiling toluene in the presence of catalytic amounts of *para*-toluenesulfonic acid (*p*-TsOH) by using a Dean-Stark trap.



Scheme 1. Preparation of fluorinated *N*-benzylnitrones **1a** and **1b**.

Several nitrone hydrates (hemiaminals) have been mentioned in the literature as intermediates [9], detected as metabolites by mass spectrometry [10] or by ^{1}H NMR spectroscopy as compounds with low stability existing in an equilibrium with the nitrone [11]. But to the best of our knowledge, only one example, the *N*-methyl analogue of **2a**, has been isolated and characterized by spectroscopic methods [6a].

Crystallization of **2a** from hexane/diethyl ether yielded colourless crystals suitable for an X-ray crystal-structure determination, which unambiguously confirmed the structure of the nitrone hydrate (Fig. 1).

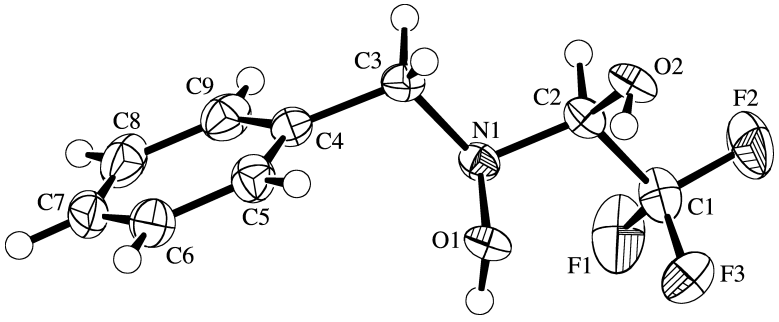
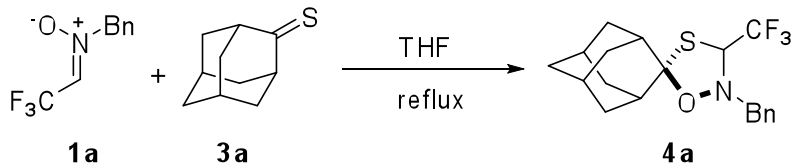


Figure 1. ORTEP plot [12] of the molecular structure of **2a** (50% probability ellipsoids; arbitrary numbering of the atoms).

The space group is centrosymmetric and, therefore, the compound in the selected crystal is racemic. The hydroxy group bonded to the N-atom forms an intermolecular hydrogen bond with the other hydroxy group of an adjacent molecule and thus links the molecules into extended chains which run parallel to the [100] direction and can be described by a graph set motif [13] of C(5). The second hydroxy group forms an intermolecular hydrogen bond with the N–OH O-atom of a centrosymmetrically related molecule and thus links pairs of molecules into centrosymmetric dimers in which the $R_2^2(10)$ hydrogen bond motif is discernable. The combination of both interactions links the molecules into ladders, which run in the [100] direction. Within the rungs of the ladders, the aforementioned $R_2^2(10)$ motif alternates with a $R_4^4(8)$ motif.

In a first experiment, a mixture of equimolar amounts of nitrone **1a** and adamantanethione (**3a**) in THF solution was heated at reflux for 3 h until the orange-red color of the thioketone disappeared. The ^{1}H NMR analysis of the crude mixture indicated the presence of the expected 1,4,2-oxathiazolidine **4a** (Scheme 2). The characteristic AB-system of the benzylic CH_2 group of **4a** appeared at 4.22 and 4.29 ppm with J_{AB} = 12.6 Hz. The isolation of the product was achieved by chromatographic workup to give **4a** in 83% yield (Table 1). The spectroscopic data proved the structure of **4a**. For example, in the ^{13}C NMR spectrum, the characteristic quartet of the CF_3 group absorbed at 123.5 ppm with $^1J_{C,F}$ = 277.9 Hz. A second quartet attributed to C(3) appeared at 72.3 ppm with $^2J_{C,F}$ = 33.4 Hz. The C(5) atom gave a singlet located at 109.2 ppm, corresponding to the chemical shift of the C(2) atom of 1,3-oxathiols [8a–c] and 1,3-oxathiolanes [8d,e]. Finally, the molecular structure of **4a** was established by X-ray crystallography (Fig. 2). Since the space group is centrosymmetric, the compound in the crystal is racemic.



1a **3a** **4a**

Scheme 2. 1,3-Dipolar cycloaddition of nitrone **1a** with adamantanethione (**3a**)

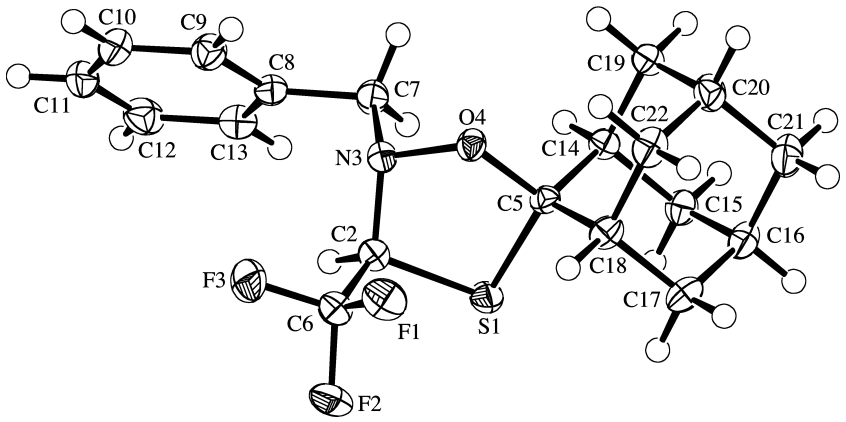
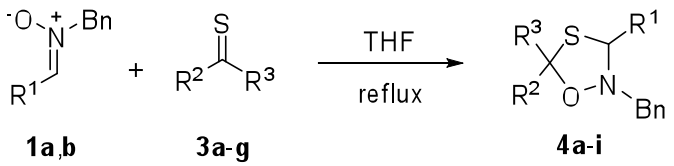


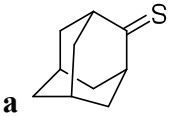
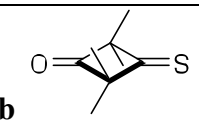
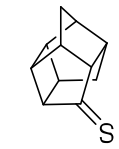
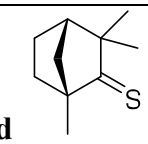
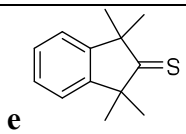
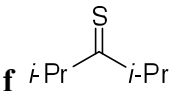
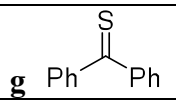
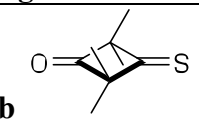
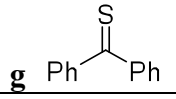
Figure 2. ORTEP plot [9] of the molecular structure of **4a** (50% probability ellipsoids; arbitrary numbering of the atoms).

Under analogous conditions, nitrone **1a** reacted chemoselectively with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**3b**) to give the desired 1,4,2-oxathiazolidine **4b** in 72% yield (Table 1). Unexpectedly, the [2+3] cycloaddition of **1a** with the 'cage thioketone' **3c** in refluxing THF was completed already after 30 min, and the ^{1}H NMR analysis of the crude product revealed the presence of two diastereoisomeric cycloadducts **4c** in a ratio of 3:2. The ratio was calculated based on intensities of two well-separated quartets at 5.17 and 5.25 ppm. These signals are attributed to H-C(3) of the heterocyclic moiety of the two isomers. The attempted separation of the isomers using column chromatography or by fractional crystallization was not successful. Similarly, the experiment with thiofenchone (**3d**) led to a 7:3 mixture of two diastereoisomeric products. The major isomer was separated chromatographically as a pure substance. Also in the case of the sterically hindered 1,1,3,3-tetramethylindane-2-thione (**3e**) in boiling THF, the expected 1,4,2-oxathiazolidine **4e** was obtained in good yield (75%, Table 1). Finally, the enolizable diisopropyl thioketone (**3f**) was reacted with **1a** yielding the cycloadduct **4f**.



Scheme 3. Reactions of nitrones **1a**,**b** with thiones **3**.

Table 1. Reaction of fluorinated nitrones **1a**,**b** with thioketones **3** in THF at reflux

Entry	R^1	Thioketone **3**	Reaction time [h]	Product	Yield [%]
1	CF_3	 **a**	3	**4a**	83
2	CF_3	 **b**	3	**4b**	72
3	CF_3	 **c**	0.5	**4c**	85
4	CF_3	 **d**	3	**4d**	75
5	CF_3	 **e**	3	**4e**	75
6	CF_3	 **f**	3	**4f**	55
7	CF_3	 **g**	3	**4g**	71
8	CHF_2	 **b**	4	**4h**	89
9	CHF_2	 **g**	4[a)]	**4i**	72

[a)] Reaction carried out in 1,2-dichloroethane

Similar to thioketones **3a**–**3f**, thiobenzophenone (**3g**) reacted with **1a** in boiling THF, and after 3 h, the blue colour of the solution disappeared, indicating completion of the reaction. The ^{1}H NMR analysis of the crude material confirmed the regioselective formation of the cycloadduct **4g** (Table 1). Based on the observed reaction times (decoloration of the solution), we concluded that the reactivity of **3g** towards **1a** is comparable with that of cycloaliphatic representatives. To prove this hypothesis, a competition experiment with equimolar amounts of **1a**, **3a**, and **3g** in THF solution was performed at room temperature to compare qualitatively the reactivity of the two thioketones under these conditions. After 3 h, the nitrone **1a** was consumed completely and the ^{1}H NMR analysis of the crude mixture evidenced the presence of cycloadducts **4a** and **4g** in a ratio of ca. 9:1. This result proves, that in contrast to reactions with thiobenzophenone *S*-methanide [4c], the cycloaliphatic **3a** is more reactive towards **1a** than the aromatic **3g**.

In another experiment, **1a** was reacted with 9*H*-fluorene-9-thione, which is known as the most reactive thioketone in reactions with diphenyldiazomethane [4b] and thiocarbonyl *S*-methanides [4c]. In this case, the undesired conversion of fluorenethione to the known bis-fluorenylidene was observed, and only in the case of a three-fold excess of 9*H*-fluorene-9-thione, the conversion of **1a** was complete. Unfortunately, the attempted separation of the cycloadduct formed thereby was unsuccessful.

Unexpectedly, the attempted reaction of **1a** with bis-(thiophen-2-yl)thioketone as a representative of hetaryl thioketones was unsuccessful at room temperature as well as at 60 °C in a closed tube (THF solution). The formation of a complex mixture of unidentified products was observed.

As an extension of the study of 1,3-dipolar cycloadditions of thioketones with fluorinated nitrones, reactions of *N*-benzyl-*C*-difluoromethylnitrone (**1b**) with the cycloaliphatic thioketone **3b** as well as with thiobenzophenone (**3g**) were carried out. Using similar reaction conditions as in the case of the reactions with **1a**, the desired cycloadducts **4h** and **4i**, respectively, were obtained in high yields. In the case of **4h**, the presence of the CHF_2 group was reflected by a *t*×*d* signal located at 5.44 ppm with $^{2}J_{H,F}$ = 58.6 Hz and $^{3}J_{H,H}$ = 6.6 Hz. In the cycloadduct **4i**, the corresponding signal was observed at 5.43 ppm ($^{2}J_{H,F}$ = 55.0 Hz, $^{3}J_{H,H}$ = 7.1 Hz).

The stability of cycloadducts **4** containing the CF_3 group at C(3) deserves a comment. Analogous cycloadducts obtained with the cycloaliphatic thioketones **2a, 2b** and *N*-methyl-*C*-phenylnitrone or with *N*-methyl-*C,C*-diphenylnitrone were reported as labile compounds, which in solution existed in an equilibrium with the 1,3-dipole and the dipolarophile [4a,14]. In some instances, secondary reactions initiated by a cycloreversion were also observed. In contrast, the fluorinated 1,4,2-oxathiazolidines **4** display a remarkable stability, and at room temperature in solution did not equilibrate with the starting materials **1** and **3**. However, heating of crystalline cycloadducts **4g** or **4i**, derived from thiobenzophenone, to the melting point, led to the formation of blue coloured liquids indicating release of **3g**.

3. Conclusions

Despite the fact that 1,3-dipolar cycloadditions of nitrones with cycloaliphatic thioketones **3a** and **3b** belong to the first described cases of 1,3-dipolar cycloadditions using C=S dipolarophiles [15], they were explored in the synthesis of S-heterocycles only to a limited extent. The main reason was the rather low reactivity of classical nitrones towards thioketones and the instability of the formed products [14]. In the case of 2-unsubstituted imidazole *N*-oxides, which are also considered as a type of aldonitrones, the reaction with 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**3b**) occurs smoothly at room temperature, but the initially formed [2+3]-cycloadduct spontaneously undergoes a ring-fragmentation yielding the corresponding imidazole-2-thione [16]. This reaction sequence is known as a ‘sulfur-transfer reaction’ with great importance for the preparation of some biologically active compounds [16b,c].

Reactions with fluorinated nitrones are rarely described, but the present study shows that, in addition to C=C and C≡C dipolarophiles [6a,b], thioketones are also attractive dipolarophiles leading to the expected 1,4,2-oxathiazolidines **4** in a regioselective manner. Perfluorinated alkyl groups, *e.g.* the trifluoromethyl group, are known to enhance the thermal stability of organic compounds, especially of strained molecules [17]. The present study shows that the CF_3 and CHF_2 groups significantly stabilize the 1,4,2-oxathiazolidine ring and, therefore, enable their exploration in organic synthesis either as target molecules or as building blocks for the preparation of

more complex systems. This is an important issue as fluorinated heterocycles found applications as drugs, agrochemicals, and materials with special properties [18].

4. Experimental part

4.1. General information

The ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded on a Bruker Avance III 600 spectrometer using the solvent signal as a reference. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. The IR spectra were measured using a NEXUS FT-IR spectrophotometer. The ESI-MS spectra were obtained using a Varian 500 MS LC Ion Trap spectrometer. Melting points were determined in a capillary on a Melt-Temp II apparatus.

4.2. Materials

Commercial trifluoroacetaldehyde hydrate and difluoroacetaldehyde ethyl hemiacetal were purchased from *Fluorochem*. *N*-Benzyl hydroxylamine was prepared from benzaldehyde based on literature procedure [19]. Thioketones were synthesized according to the known protocols: adamantanethione (**3a**) [20], 2,2,4,4-tetramethyl-3-thioxocyclobutanone (**3b**) [21], 'cage' thioketone (**3c**) [22], diisopropyl thioketone (**3d**) [23], 1,1,3,3-tetramethylindane-2-thione (**3e**) [24], thiofenchone (**3f**) [25], thiobenzophenone (**3g**) [26], and thiofluorenone [27].

4.3. Synthesis of fluorinated nitrones

N-Benzyl-N-(2,2,2-trifluoro-1-hydroxyethyl)hydroxylamine (N-Benzyl C-(trifluoromethyl)nitrone hydrate; **2a**).Trifluoroacetaldehyde hydrate (70%) (1.08g, 6.5 mmol) was added to a solution of freshly prepared *N*-benzylhydroxylamine (615 mg, 5 mmol) in dichloromethane (10 ml). The reaction was carried out in the presence of molecular sieves 4 Å for 40 min. Then, an additional portion of drying agent (Na_2SO_4) was added. After filtration, the solvent was evaporated and crude hemiaminal **2a** was obtained as a colorless, crystalline material in nearly quantitative yield (1.01g). An analytically pure sample was obtained by crystallization from hexane/Et_2O (m.p. 92-94 °C). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.85 (br. s, 1H, OH), 4.01, 4.20 (2d, $^{2}J_{H,H}$ = 12.6 Hz, 2H, CH_2), 4.53 (q, $^{3}J_{H,F}$ = 5.5 Hz, 1H, CH), 7.33–7.41 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 59.9 (CH_2), 83.4 (q, $^{2}J_{C,F}$ = 32.1 Hz, CH), 122.6 (q, $^{1}J_{C,F}$ = 281.7

Hz, CF_3), 128.0, 128.6, 129.4 (5 arom. CH), 135.7 (1 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –78.3 (d, $^3J_{H,F}$ = 5.5 Hz, 3F, CF_3). **IR** (KBr): *v* 3386*br.vs*, 3313*br.vs*, 3034*w*, 2955*w*, 2916*w*, 2855*w*, 1636*br.m*, 1457*m*, 1399*m*, 1351*m*, 1287*s*, 1192*vs*, 1153*vs*, 1100*m*, 1043*s*, 954*w*, 827*m*. HR-EI-MS: 221.06589 (221.06581 calcd. for $C_9H_{10}F_3NO_2$, $[M]^+$).

N-Benzyl C-(trifluoromethyl)nitrone (**1a**) [6d]. Crude hemiaminal **2a** was suspended in toluene (15 ml) and a catalytic amount of *p*-TsOH·H_2O (19 mg, 0.1 mmol) was added. The mixture was heated at reflux in a Dean-Stark apparatus. After ca. 1 h water was completely removed and the solvent was evaporated. Pure product was obtained after crystallization from hexane 528 mg (52%; based on benzylhydroxylamine used), m.p. 65-67 °C (hexane). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.02 (s, 2H, CH_2), 6.87 (q, $^3J_{H,F}$ = 5.5 Hz, 1H, CH), 7.41–7.49 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 71.8 (CH_2), 119.5 (q, $^1J_{C,F}$ = 268.3 Hz, CF_3), 123.5 (q, $^2J_{C,F}$ = 37.3 Hz, CH), 129.4, 129.7, 129.9 (5 arom. CH), 130.9 (1 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –65.9 (d, $^3J_{H,F}$ = 5.5 Hz, 3F, CF_3). IR (KBr): *v* 3181*w*, 3103*m*, 3045*w*, 1599*s* (C=N), 1460*m*, 1218*vs*, 1150*vs*, 947*m*, 717*m*. HR-ESI-MS: 226.04484 (226.04502 calcd. for $C_9H_8F_3NNaO$, $[M+Na]^+$).

N-Benzyl C-(difluoromethyl)nitrone (**1b**). Difluoroacetaldehyde ethyl hemiacetal (819 mg, 6.5 mmol) was added to a solution of freshly prepared *N*-benzyl-hydroxylamine (615 mg, 5 mmol) and a catalytic amount of *p*-TsOH·H_2O (19 mg, 0.1 mmol) in toluene (10 ml). The mixture was heated at reflux in a Dean-Stark apparatus until evolution of water was finished (ca. 1 h), and then the solvent was evaporated. Pure product was obtained after crystallization from hexane 894 mg (84%), m.p. 60–62 °C (hexane). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.97 (s, 2H, CH_2), 6.72 (td, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,H}$ = 5.4 Hz, 1H, CH), 6.88 (td, $^3J_{H,F}$ = $^3J_{H,H}$ = 5.4 Hz, 1H, CHF_2), 7.43–7.48 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 70.7 (CH_2), 108.7 (t, $^1J_{C,F}$ = 231.3 Hz, CHF_2), 130.0 (t, $^2J_{C,F}$ = 35.4 Hz, CH), 129.3, 129.6, 129.7 (5 arom. CH), 131.2 (1 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ 121.6 (dd, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,H}$ = 5.4 Hz, 2F, CHF_2). IR (KBr): *v* 3184*w*, 3090*s*, 3036*m*, 1597*vs* (C=N), 1459*vs*, 1434*s*, 1307*s*, 1200*s*, 1212*s*, 1119*vs*, 1042*vs*, 932*m*, 908*m*, 706*vs*. HR-ESI-MS: 208.05428 (208.05444 calcd. for $C_9H_9F_2NNaO$, $[M+Na]^+$).

4.4. Reactions of fluorinated nitrones with thioketones – general procedure

A solution of thioketone **2** (0.5 mmol) and nitrone **1** (0.55 mmol) in an appropriate solvent (2 ml) was heated under reflux until the color of **2** completely disappeared (see *Table 1*). Analytically pure products were obtained after crystallization from an appropriate solvent, column chromatography or purification by preparative layer chromatography (PLC).

2-Benzyl-3-trifluoromethylspiro[1,4,2-oxathiazolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (**4a**). Yield: 153 mg (83%), colorless crystals, m.p. 126–128 °C (hexane/Et_2O). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.57–1.70, 1.76–1.77, 1.87–1.90, 2.00–2.04, 2.15–2.16, 2.25–2.26 (6m, 14H, adamantane), 4.22, 4.29 (2d, $^2J_{H,H}$ = 12.6 Hz, 2H, PhC**H**$_2$), 4.58 (q, $^3J_{H,F}$ = 7.2 Hz, 1H, CH), 7.22–7.29 (m, 3 arom. CH), 7.32–7.33 (m, 2 arom. CH). ^{13}C-NMR (151 MHz, $CDCl_3$): δ 25.9, 26.4, 34.2, 34.9, 37.1, 38.1, 38.8, 40.1, 42.9 (adamantane), 63.1 (Ph**C**H$_2$), 72.3 (q, $^2J_{C,F}$ = 33.4 Hz, **C**HCF$_3$), 109.2 (C$_q$), 123.5 (q, $^1J_{C,F}$ = 277.9 Hz, CF$_3$), 128.1, 128.6, 128.9 (5 arom. CH), 135.8 (1 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –73.4 (d, $^3J_{H,F}$ = 7.2 Hz, 3F, CF$_3$). IR (KBr): *v* 2947*s*, 2930*s*, 2913*s*, 2863*s*, 1456*m*, 1366*s*, 1281*vs*, 1212*s*, 1162*vs*, 1119*vs*, 1100*s*, 982*m*, 890*m*, 749*s*, 699*s*. HR-ESI-MS: 392.12654 (392.12664 calcd. for $C_{19}H_{22}F_3NNaOS$, $[M+Na]^+$), 370.14477 (370.14470 calcd. for $C_{19}H_{23}F_3NOS$, $[M+H]^+$).

6-Benzyl-1,1,3,3-tetramethyl-7-trifluoromethyl-5-oxa-6-aza-8-thiaspiro[3.4]octane (**4b**). Yield: 129 mg (72%), colorless crystals, m.p. 102–105 °C (hexane). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.17, 1.23, 1.25 (3s, 12H, 4 CH$_3$), 3.80, 4.22 (2d, $^2J_{H,H}$ = 12.0 Hz, 2H, PhC**H**$_2$), 4.56 (q, $^3J_{H,F}$ = 6.8 Hz, 1H, C**H**CF$_3$), 7.25–7.33 (m, 5 arom. CH). ^{13}C-NMR (151 MHz, $CDCl_3$): δ 18.6, 20.8, 22.2, 24.1 (4 CH$_3$), 62.1 (Ph**C**H$_2$), 65.8, 67.2 (2 C$_q$), 71.8 (q, $^2J_{C,F}$ = 34.5 Hz, **C**HCF$_3$), 105.4 (C$_q$), 122.9 (q, $^1J_{C,F}$ = 277.5 Hz, CF$_3$), 128.6, 128.9, 129.2 (5 arom. CH), 134.3 (1 arom. C), 218.9 (C=O). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –74.0 (d, $^3J_{H,F}$ = 6.8 Hz, 3F, CF$_3$). IR (KBr): *v* 3033*m*, 2988*w*, 2973*m*, 2936*w*, 2872*w*, 1790*vs*, 1774*vs*, 1462*s*, 1433*w*, 1364*m*, 1356*m*, 1281*vs*, 1165*vs*, 1128*vs*, 1027*s*, 890*w*, 743*m*, 698*s*. HR-ESI-MS: 382.10606 (382.10591 calcd. for $C_{17}H_{20}F_3NNaO_2S$, $[M+Na]^+$).

2-Benzyl-3-trifluoromethylspiro[1,4,2-oxathiazolidie-5,8'-pentacyclo[5.4.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**4c**). Yield: 161 mg, m.p. 150-153 °C (without

crystallization; after PLC, isolated as a 6:4 mixture of unseparable diastereoisomers). ^{1}H-NMR (600 MHz, $(CD_3)_2CO$: δ major diastereoisomer 4.21, 4.25 (2d, $^{2}J_{H,H}$ = 12.6 Hz, 2H, PhC**H**$_2$), 5.17 (q, $^{3}J_{H,F}$ = 5.5 Hz, 1H, CH); minor diastereoisomer 4.28, 4.32 (2d, $^{2}J_{H,H}$ = 12.6 Hz, 2H, PhC**H**$_2$), 5.25 (q, $^{3}J_{H,F}$ = 5.5 Hz, 1H, CH); both diastereoisomers 1.25–1.30, 1.69–1.73, 2.07–2.08, 2.29–2.77, 2.93–2.96 (5m, 12H, 'cage'), 7.31–7.47 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $(CD_3)_2CO$): δ major diastereoisomer: 61.9 (Ph**C**H$_2$), 73.0 (q, $^{2}J_{C,F}$ = 33.0 Hz, **C**HCF$_3$), 105.7 (C$_q$), 123.7 (q, $^{1}J_{C,F}$ = 277.5 Hz, **C**F$_3$), 127.8, 128.4, 128.9 (5 arom. CH), 136.1 (1 arom. C); minor diastereoisomer: 62.1 (Ph**C**H$_2$), 73.3 (q, $^{2}J_{C,F}$ = 33.0 Hz, **C**HCF$_3$), 105.8 (C$_q$), 123.8 (q, $^{1}J_{C,F}$ = 277.5 Hz, **C**F$_3$), 127.7, 128.3, 128.8 (5 arom. CH), 136.2 (1 arom. C); both diastereoisomers: 34.0, 34.2 (2 CH$_2$ each isomer), 35.0, 35.5, 41.1, 41.59, 41.68, 41.71, 41.8, 42.6, 45.56, 45.63, 45.69, 46.7, 47.0, 47.7, 52.9, 55.9 (8 CH for each isomer). ^{19}F-NMR (565 MHz, $(CD_3)_2CO$): δ major isomer –74.7 (d, $^{3}J_{H,F}$ = 5.5 Hz, 3F, CF$_3$), minor isomer –74.9 (d, $^{3}J_{H,F}$ = 5.5 Hz, 3F, CF$_3$). IR (KBr): *v* 2972*vs*, 2988*vs*, 2872*m*, 1452*m*, 1364*s*, 1281*vs*, 1212*s*, 1163*vs*, 1118*vs*, 1092*s*, 1029*m*, 976*m*, 890*m*, 699*s*. HR-ESI-MS: 402.11099 (402.11133 calcd. for $C_{20}H_{20}F_3NNaOS$, $[M+Na]^+$), 380.12905 (380.12905 calcd. for $C_{20}H_{21}F_3NOS$, $[M+H]^+$).

2-Benzyl-1',3',3'-trimethyl-3-trifluoromethylspiro[1,4,2-oxathiazolidine-5,2'-norbornane (obtained as the 7:3 mixture of diastereoisomers **4d** and **4d'**). Yield after chromatography (SiO_2, hexane): 80 mg (45%) of major isomer **4d** (fast moving), 56 mg (30%) of a mixture of diastereoisomers **4d** and **4d'**, colorless oils. Data of **4d:** ^{1}H-NMR (600 MHz, $CDCl_3$): 0.85, 1.13, 1.18 (3s, 9H, 3CH$_3$), 1.13–1.14 (m, 2H, fenchon), 1.38–1.39 (m, 2H, fenchon), 1.63–1.67 (m, 1H, fenchon), 1.70–1.71 (m, 2H, fenchon), 3.98, 4.36 (2d, $^{2}J_{H,H}$ = 13.8 Hz, 2H, PhC**H**$_2$), 4.39 (q, $^{3}J_{H,F}$ = 4.9 Hz, 1H, CH), 7.31–7.37 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 16.8, 23.2, 25.3 (3 CH$_3$), 27.9 (CH), 34.9, 41.1, 49.0 (3 CH$_2$), 48.0, 52.7 (2 C$_q$), 61.4 (Ph**C**H$_2$), 70.5 (q, $^{2}J_{C,F}$ = 29.7 Hz, **C**HCF$_3$), 108.7 (C$_q$), 124.1 (q, $^{1}J_{C,F}$ = 276.9 Hz, CF$_3$), 127.7, 127.9, 130.3 (5 arom. CH), 135.2 (1 arom. **C**). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –68.8.7 (d, $^{3}J_{H,F}$ = 4.9 Hz, 3F, CF$_3$). IR (KBr): *v* 3090*w*, 3066*m*, 2974*s*, 2941*s*, 1497*m*, 1486*m*, 1455*m*, 1368*m*, 1343*m*, 1274*s*, 1162*s*, 1123*s*, 1050*m*, 993*m*, 753*m*, 698*s*. HR-ESI-MS: 394.14193 (394.14229 calcd. for $C_{19}H_{24}F_3NNaOS$, $[M+Na]^+$), 372.16032 (372.16035 calcd. for $C_{19}H_{25}F_3NOS$, $[M+H]^+$).

2-Benzyl-1',1',3',3'-tetramethyl-3-trifluoromethylspiro[1,4,2-oxathiazolidine-5,2'-indane] (**4e**). Yield: 152 mg (75%), colorless oil (hexane/SiO_2). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.21, 1.27, 1.28, 1.32 (4s, 12H, 4 CH_3), 3.92, 4.28 (2d, $^2J_{H,H}$ = 14.4 Hz, 2H, PhC**H**$_2$), 4.45 (q, $^3J_{H,F}$ = 5.1 Hz, 1H, CH), 7.00–7.02 (m, 2 arom. CH), 7.09–7.12 (m, 3 arom. CH), 7.15–7.17 (m, 4 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 23.2, 24.1, 31.5, 32.7 (4 CH_3), 50.5, 52.1 (2 C_q), 60.4 (Ph**C**H_2), 69.5 (q, $^2J_{C,F}$ = 29.8 Hz, **C**HCF_3), 109.7 (C_q), 121.9, 122.7, 127.0, 127.2, 127.8, 128.1, 130.1 (9 arom. CH), 124.0 (q, $^1J_{C,F}$ = 277.8 Hz, **C**F_3), 134.6, 147.2, 148.3 (3 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –68.5 (d, $^3J_{H,F}$ = 5.1 Hz, 3F, CF_3). IR (KBr): *v* 3066*m*, 3033*s*, 2967*vs*, 2930*vs*, 2867*s*, 1733*m*, 1589*m*, 1482*s*, 1455*s*, 1381*s*, 1366*s*, 1346*s*, 1271*vs*, 1158*vs*, 1124*vs*, 1051*s*, 982*s*, 892*s*. HR-ESI-MS: 430.14226 (430.14229 calcd. for $C_{22}H_{24}F_3NNaOS$, $[M+Na]^+$), 408.16035 (408.16035 calcd. for $C_{22}H_{25}F_3NOS$, $[M+H]^+$).

2-Benzyl-5,5-diisopropyl-3-trifluoromethyl-1,4,2-oxathiazolidine (**4f**). Yield: 92 mg (55%), colorless oil (hexane/SiO_2). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.79, 0.89, 0.91, 0.97 (4d, $^3J_{H,H}$ = 7.2 Hz, 12H, 4 CH_3), 2.11–2.18, 2.47–2.54 (2m, 2H, 2 CH), 4.93, 4.27 (2d, $^2J_{H,H}$ = 13.8 Hz, 2H, PhC**H**$_2$), 4.40 (q, $^3J_{H,F}$ = 5.2 Hz, 1H, CH), 7.16–7.27 (m, 5 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 18.4, 18.6, 19.1, 20.7 (4 CH_3), 32.4, 37.4 (2 CH), 60.9 (Ph**C**H_2), 71.1 (q, $^2J_{C,F}$ = 29.8 Hz, **C**HCF_3), 105.2 (C_q), 124.0 (q, $^1J_{C,F}$ = 277.3 Hz, CF_3), 127.5, 128.1, 129.2 (5 arom. CH), 136.2 (1 arom. **C**). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –68.7 (d, $^3J_{H,F}$ = 5.2 Hz, 3F, CF_3). IR (KBr): *v* 3091*w*, 3066*w*, 2968*m*, 2936*m*, 2876*m*, 1497*w*, 1456*m*, 1386*m*, 1344*m*, 1272*m*, 1161*m*, 1123*m*, 1030*w*, 889*w*, 696*m*. HR-ESI-MS: 356.12683 (356.12664 calcd. for $C_{16}H_{22}F_3NNaOS$, $[M+Na]^+$), 334.14488 (334.14470 calcd. for $C_{16}H_{23}F_3NOS$, $[M+H]^+$).

2-Benzyl-5,5-diphenyl-3-trifluoromethyl-1,4,2-oxathiazolidine (**4g**). Yield: 142 mg (71%), colorless crystals, m.p. 132–134 °C (hexane/Et_2O). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.84, 4.18 (2d, $^2J_{H,H}$ = 13.0 Hz, 2H, PhC**H**$_2$), 4.94 (q, $^3J_{H,F}$ = 6.6 Hz, 1H, CH), 7.23–7.38 (m, 11 arom. CH), 7.44–7.46 (m, 2 arom. CH), 7.63–7.65 (m, 2 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 63.0 (Ph**C**H_2), 73.9 (q, $^2J_{C,F}$ = 34.5 Hz, **C**HCF_3), 105.2 (C_q), 123.3 (q, $^1J_{C,F}$ = 279.0 Hz, CF_3), 126.2, 126.7, 127.7, 128.0, 128.2, 128.3, 128.6, 129.1 (15 arom. CH), 135.1, 143.4, 144.8 (3 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –73.3 (d, $^3J_{H,F}$ = 6.6 Hz, CF_3). IR (KBr): *v* 3061*w*, 3031*w*, 2925*w*, 1491*m*, 1447*m*, 1357*s*, 1276*vs*, 1168*vs*, 1116*vs*, 1096*s*, 952*m*, 910*m*, 742*s*, 697*vs*. HR-ESI-MS:

440.06947 (440.06928 calcd. for $C_{22}H_{18}F_2KNOS$, $[M+K]^+$), 424.09580 (424.09528 calcd. for $C_{22}H_{18}F_2NNaOS$, $[M+Na]^+$), 402.11338 (402.11340 calcd. for $C_{22}H_{19}F_3NOS$, $[M+1]^+$).

6-Benzyl-1,1,3,3-tetramethyl-7-difluoromethyl-5-oxa-6-aza-8-thiaspiro[3.4]-octane (**4h**). Yield: 151 mg (89%), colorless crystals, m.p. 67–70 °C (hexane). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.13, 1.22, 1.23, 1.25 (4s, 12H, 4 CH_3), 3.87, 4.15 (2d, $^2J_{H,H}$ = 12.0 Hz, 2H, PhC**H**$_2$), 4.39–4.43 (m, 1H, C**H**CHF$_2$), 5.44 (dt, $^3J_{H,H}$ = 6.6 Hz, $^2J_{H,F(1)}$ = $^2J_{H,F(2)}$ = 58.6 Hz, 1H, CHC**H**F$_2$), 7.25–7.31 (m, 5 arom. CH). ^{13}C-NMR (151 MHz, $CDCl_3$): δ 18.5, 20.6, 22.3, 24.6 (4 CH_3); 61.4 (Ph**C**H$_2$), 65.6, 66.9 (2 C_q), 73.3 (dd, $^2J_{C,F(1)}$ = $^2J_{C,F(2)}$ = 25.5 Hz, **C**HCHF$_2$), 104.3 (C_q), 113.6 (dd, $^1J_{C,F(1)}$ = 246.0 Hz, $^1J_{C,F(2)}$ = 241.5 Hz, CH**C**HF$_2$), 128.4, 128.8, 129.3 (5 arom. CH), 134.6 (2 arom. C), 219.0 (C=O). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –117.2 (ddd, $^2J_{F,F}$ = 282.5 Hz, $^2J_{H,F}$ = 58.6 Hz, $^3J_{H,F(1)}$ = 7.9 Hz, 1F, CHCHF$_2$), –124.2. (ddd, $^2J_{F,F}$ = 282.5 Hz, $^2J_{H,F}$ = 58.6 Hz, $^3J_{H,F(2)}$ = 10.2 Hz, 1F, CHCHF$_2$). IR (KBr): *ν* 3032*w*, 2990*m*, 2977*s*, 2933*m*, 1790*vs*, 1777*vs*, 1461*s*, 1383*s*, 1365*m*, 1255*m*, 1106*vs*, 1056*vs*, 1031*s*, 864*m*, 698*s* cm^{-1}. HR-ESI-MS: 364.11560 (364.11533 calcd. for $C_{17}H_{21}F_2NNaO_2S$, $[M+Na]^+$).

2-Benzyl-5,5-diphenyl-3-difluoromethyl-1,4,2-oxathiazolidine (**4i**). Yield: 138 mg (72%), colorless crystals, 108–110 °C (hexane/E_2O, decomp.). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.86, 4.09 (2d, $^2J_{H,H}$ = 12.4 Hz, 2H, PhCH_2), 4.66 (q, $^3J_{H,H}$ = $^3J_{H,F(1)}$ = $^3J_{H,F(2)}$ = 6.5 Hz, 1H, C**H**CHF$_2$), 5.43 (dt, $^3J_{H,H}$ = 7.1 Hz, $^2J_{H,F(1)}$ = $^2J_{H,F(2)}$ = 55.0 Hz, 1H, CHC**H**F$_2$), 7.16–7.24 (m, 11 arom. CH), 7.35–7.37 (m, 2 arom. CH), 7.43–7.46 (m, 2 arom. CH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 62.1 (Ph**C**H$_2$), 75.8 (dd, $^2J_{C,F(1)}$ = 28.5 Hz, $^2J_{C,F(2)}$ = 22.5 Hz **C**HCHF$_2$), 104.2 (C_q), 113.6 (dd, $^2J_{C,F(1)}$ = 249.0 Hz, $^2J_{C,F(2)}$ = 238.5 Hz, CH**C**HF$_2$), 126.0, 126.4, 127.3, 128.0, 128.1, 128.2, 128.3, 128.5, 129.1 (15 arom. CH), 135.5, 144.2, 144.7 (3 arom. C). ^{19}F-NMR (565 MHz, $CDCl_3$): δ –115.7, –124.6 (2ddd, $^2J_{F,F}$ = 280.8 Hz, $^2J_{H,F}$ = 55.0 Hz, $^3J_{H,F}$ = 6.5 Hz, CHCHF$_2$). IR (KBr): *ν* 3084*w*, 3053*w*, 3029*w*, 2932*w*, 1495*m*, 1446*s*, 1394*m*, 1230*w*, 1104*vs*, 1069*s*, 1051*vs*, 911*m*, 751*vs*, 702*vs*. HR-ESI-MS: 406.10476 (406.10508 calcd. for $C_{12}H_{19}F_2NNaOS$, $[M+Na]^+$).

4.6. X-ray crystal-structure determinations of **2** *and* **4a**

All measurements for **4a** were performed on a Nonius KappaCCD area-detector diffractometer [28] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and

an Oxford Cryosystems Cryostream 700 cooler, those for **2** on an Agilent Technologies SuperNova area detector diffractometer [29] using MoK_α radiation (λ 0.71073 Å) from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler. The data collection and refinement parameters are given below [30] and views of the molecules are shown in Figures 1 and 2. Data reduction for **4a** was performed with HKL Denzo and Scalepack [31], for **2** with CrysAlisPro [29]. The intensities were corrected for Lorentz and polarization effects, and absorption corrections based on the multi-scan method [29,32] were applied. Equivalent reflections were merged. The structure was solved by direct methods using SHELXS97 [33] in the case of **4a** and SHELXS-2013 [34] in the case of **2**, which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydroxy H-atoms of **2** were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All H-atoms of **4a** and all remaining H-atoms of **2** were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom. The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Corrections for secondary extinction were not applied. In the case of **4a**, three reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from ref. [35], and the scattering factors for H-atoms were taken from ref. [36] Anomalous dispersion effects were included in F_c [37]; the values for f' and f'' were those of ref. [38]. The values of the mass attenuation coefficients are those of ref. [39]. All calculations were performed using the SHELXL97 [33] program in the case of **4a** and SHELXS-2013 [34] in the case of **2**.

Crystal data for **4a**: $C_{19}H_{22}F_3NOS$, M = 369.44, crystallised from hexane/Et_2O/CH_2Cl_2, colourless, prism, crystal dimensions 0.23 × 0.26 × 0.28 mm, triclinic, space group $P\bar{1}$, Z = 2, reflections for cell determination 27238, 2θ range for cell determination 4 – 60°, a = 6.7469(1) Å, b = 9.7074(1) Å, c = 14.0136(2) Å, α = 93.6106(9), β = 101.2555(8), γ = 104.3345(9), V = 866.14(2) Å^3, T = 160(1) K, D_X = 1.416 g·cm^{-3}, μ(MoK_α) = 0.224 mm^{-1}, scan type ϕ and ω, 2$\theta_{(max)}$ = 60°, transmission factors (min; max) 0.886; 0.951, total reflections measured 23398, symmetry

independent reflections 5049, reflections with $I > 2\sigma(I)$ 4180, reflections used in refinement 5046, parameters refined 226; $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0393, $wR(F^2)$ [all data] = 0.1035 ($w = [\sigma^2(F_o^2)+ (0.0475P)^2+0.2969P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.046, final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.36; –0.31 e Å^{-3}.

Crystal data for **2**: $C_9H_{10}F_3NO_2$, M = 221.18, crystallised from hexane/Et_2O, colourless, prism, crystal dimensions 0.12 × 0.14 × 0.25 mm, monoclinic, space group $P2_1/c$, Z = 4, reflections for cell determination 3760, 2θ range for cell determination 5 – 56°, a = 5.0986(3) Å, b = 11.4367(6) Å, c = 17.2009(12) Å, β = 95.969(7), V = 997.58(11) Å^3, T = 160(1) K, D_X = 1.473 g·cm^{-3}, μ(MoK_α) = 0.140 mm^{-1}, scan type ω, $2\theta_{(max)}$ = 56.6°, transmission factors (min; max) 0.765; 1.000, total reflections measured 9341, symmetry independent reflections 2222, reflections with $I > 2\sigma(I)$ 1598, reflections used in refinement 2222, parameters refined 144; $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0527, $wR(F^2)$ [all data] = 0.1386 ($w = [\sigma^2(F_o^2)+ (0.0657P)^2+0.2604P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.051, final Δ_{max}/σ 0.000, $\Delta\rho$ (max; min) = 0.21; –0.31 e Å^{-3}.

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